REMARKS

In reply to the Office Action mailed March 19, 2009, Applicants cancelled claim 113. Claims 86, 94-98, 100-102, 110-112, and 114-119 are pending and under examination. Please consider the following remarks.

Rejections Under 35 U.S.C. §103

Claims 86, 100-102 and 110-119 were rejected under 35 U.S.C. §103 as being unpatentable over the combination of Kay, Fosnaugh, Frecht, and Florence. Claim 86, the only pending independent claim, recites a double-stranded ribonucleic acid (dsRNA) comprising a complementary RNA strand, a sense RNA strand and only one lipophilic group having a $\log K_{ow}$ exceeding 1. The complementary RNA strand has a nucleotide sequence which is complementary to a target RNA, and wherein the target RNA is an mRNA transcript of a target gene or of a (+) strand RNA virus. The lipophilic group is covalently attached to a 5'-end of the complementary RNA strand and a linkage between the lipophilic group and the 5'-end of the complementary RNA strand comprises a phosphodiester group.

Kay is cited for the teaching of dsRNA that efficiently inhibit viral gene expression, and targeting hepatocyte cells using a dsRNA molecule capable of inhibiting the expression of a Hepatitic C Virus. (See office Action, page 4.) Kay does not teach, nor is Kay cited for the teaching of a lipophiilic group linked at the 5' end with a phospodiester group as required by the pending claims. The Examiner cites Fosnaugh for teaching of a dsRNA that comprises a conjugate covalently attached to the dsRNA wherein the conjugate is attached to the 5' end of either strand and for the teaching that the conjugate can be linked with biodegradable linkers as well as phophodiester linkages. (Id.) Neither Frecht nor Florence disclose a lipophilic group covalently attached to a 5'-end of the complementary RNA strand wherein a linkage between the lipophilic group and the 5'-end of the complementary RNA strand comprises a phosphodiester group as recited in the pending claims, nor are they relied upon for such a teaching.

Although not cited in the currently outstanding Office Action, Applicants submit that Rana teaches away from the 5' modification of the complementary RNA strand. Moreover, the Examiner has acknowledged that "Applicant is correct in that Rana et al. teach the 5' end of the antisense strand should contain a free OH group for efficient RNA interference." (See Office Action mailed August 21, 2008, page 3.) Nowhere in the Office Action has the Examiner

provided a reasonable explanation as to why one of skill in the art would ignore this teaching, as would be required to arrive at the claimed invention.

As noted above, the Examiner relies on Fosnaugh for the teaching of a conjugate covalently attached to the 5' end of the complementary RNA strand. The portion of Fosnaugh relied upon by the Examiner for this assertion is provide below:

> In one embodiment, the invention features a chemically modified short interfering RNA (siRNA) molecule capable of mediating RNA interference (RNAi) against ADORA1 inside a cell or reconstituted in vitro system, wherein the chemical modification comprises a conjugate covalently attached to the siRNA molecule. In another embodiment, the conjugate is covalently attached to the siRNA molecule via a biodegradable linker. In one embodiment, the conjugate molecule is attached at the 3'-end of either the sense strand, antisense strand, or both strands of the siRNA. In another embodiment, the conjugate molecule is attached at the 5'-end of either the sense strand, antisense strand, or both strands of the siRNA. In yet another embodiment, the conjugate molecule is attached both the 3'-end and 5'-end of either the sense strand, antisense strand, or both strands of the siRNA, or any combination thereof. In one embodiment, a conjugate molecule of the invention comprises a molecule that facilitates delivery of a siRNA molecule into a biological system such as a cell. In another embodiment, the conjugate molecule attached to the siRNA is a poly ethylene glycol, human serum albumin, or a ligand for a cellular receptor that can mediate cellular uptake. Examples of specific conjugate molecules contemplated by the instant invention that can be attached to siRNA molecules are described in Vargeese et al., U.S. Ser. No. 60/311,865, incorporated by reference herein. (Fosnaugh [0068], Emphasis added.)

As provided in the underlined portion above, Fosnaugh simply provides a generic statement reciting multiple possible configurations of a conjugate. Moreover, Fosnaugh provides no examples of a lipophilic group covalently attached to a 5'-end of the complementary RNA strand wherein a linkage between the lipophilic group and the 5'-end of the complementary RNA strand comprises a phosphodiester group as recited in the pending claims.

Applicants submit that when evaluating the patentability of a claim, the Examiner must determine the content of the prior art as a whole. (*See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.) When reading the art as a whole, a skilled artisan would consider both Fosnaugh and Rana. Applicants submit that when considering these references together, one skilled in the art would follow the clear teaching in Rana, that "the 5' end of the

antisense strand should contain a free OH group for efficient RNA interference." This teaching is backed up by specific examples demonstrating this teaching, for example, as provided in Example IV, where Rana demonstrates that the 5' hydroxyl determines the RNAi activity and further demonstrates that modification at the 3' has little effect. In addition to the teaching in Rana, Applicants also point to the references identified in the specification, which Applicants noted provide evidence of a belief at the time of filing "that sdRNA with 5'-modifications in the antisense strand is unable to cause RNA interference." (See Application paragraph bridging pages 17 and 18 and related references cited therein.) Moreover, also in the Application, Applicants refer to the specific importance of the phosphodiester linkage, which is not evident anywhere in the art of record. (Id.)

Nothing in Fosnaugh would lead one skilled in the art to disregard this teaching, especially in light of the very generic disclosure relied upon by the Examiner, which is backed by no examples that either contradict the teaching in Rana or provide any other reason to make a double-stranded ribonucleic acid (dsRNA) comprising lipophilic group covalently attached to a 5'-end of the complementary RNA strand wherein a linkage between the lipophilic group and the 5'-end of the complementary RNA strand comprises a phosphodiester group as recited in the pending claims. In view of the above, Applicants submit that the pending claims are patentable over the combination of Kay, Fosnaugh, Frecht, and Florence and request that the corresponding rejection be withdrawn.

Claims 86, 94-98, and 110-119 were rejected under 35 U.S.C. §103 as being unpatentable over the combination of Kay, Fosnaugh, Manoharan I, and Cook and evidenced by Manoharan II. Applicants reiterate the arguments above regarding the teaching of Kay and Fosnaugh, specifically as the teachings relate to a double-stranded ribonucleic acid (dsRNA) comprising lipophilic group covalently attached to a 5'-end of the complementary RNA strand wherein a linkage between the lipophilic group and the 5'-end of the complementary RNA strand comprises a phosphodiester group. Applicants also submit that none of Manoharan I, Cook or Manoharan II disclose or teach a double-stranded ribonucleic acid (dsRNA) comprising lipophilic group covalently attached to a 5'-end of the complementary RNA strand wherein a linkage between the lipophilic group and the 5'-end of the complementary RNA strand comprises a phosphodiester group nor are they relied upon for such a teaching. For at least the reasons above, Applicants submit that one skilled in the art, when considering the art as a whole,

would not ignore the clear teachings of Rana, and therefore would not have arrived at the claimed invention based on the art of record. Applicants submit that the pending claims are patentable over the combination of Kay, Fosnaugh, Manoharan I, Cook and Manoharan II, and request that the corresponding rejection be withdrawn.

Applicants submit the application is in condition for allowance, which action is requested.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, please charge any deficiency to Deposit Account No. 50/2762, referencing Attorney's Docket No. A2038-7052US.

Respectfully submitted,
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Docket No.: A2038-7052US
Date: June 19, 2009
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